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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/473,830	12/28/99	LEIDEN J	2844/53802

HM12/0213

HALE AND DORR
60 STATE STREET
BOSTON MA 02109

EXAMINER	
DRABIK,C	
ART UNIT	**PAPER NUMBER**
1633	10

DATE MAILED: 02/13/01

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No. 09/473,830	Applicant(s) LEIDEN ET AL.	
	Examiner Christopher Drabik	Art Unit 1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02 January 2001* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-23* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-23* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

15) ☐ Notice of References Cited (PTO-892)
16) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
17) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
18) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
19) ☐ Notice of Informal Patent Application (PTO-152)
20) ☐ Other: .

Detailed Action

The text of those sections of Title 35, U.S. Code not included in this action can be found in the prior Office Action.

Claim Rejections

Claims 1-23 remain rejected under 35 USC 112 first paragraph, because the specification does not enable one skilled in the art to practice the full scope of the invention as claimed. For the reasons set forth in the previous Office Action, the invention is enabled for the use of a recombinant adeno-associated virus vector to transfer the β-galactosidase gene to mouse myocytes and in vivo expression of said gene thereto. The invention is not enabled to practice therapy involving the transfer of any other gene to any other animal.

No Claim is allowed.

Response to Arguments

Applicants arguments filed 2 January 2001 have been fully considered, but are not persuasive for the following reasons:

35 USC 112, 1st Paragraph

Applicants traverse the rejection of claims 1-23. Traversal is based on the assertion that the invention is fully enabled for the claimed method of gene therapy of

human cardiovascular conditions. The non-enablement position set forth in the prior Office Action was based on the lack of guidance and undue experimentation required to perform gene therapy in humans using the vector and methods described in the instant application.

In the response mailed on 2 January 2001 Applicants convincingly argue that the rAAV vectors and methods as described can be used for the transfer of the β-galactosidase gene into mouse cardiomyocytes. No further support for the enablement of said vectors and methods described in the instant application for use in gene therapy is provided. Applicants argue that the expression of a bacterial gene in cardiomyocytes enables the amelioration of an incompletely delineated group of cardiovascular conditions including restenosis, atherosclerosis, congestive heart failure, ischemia, cardiomyopathy, malignant arrhythmia, myocardial infarction, congestive heart failure... The examiner maintains the position that the success of using a novel vector and method for the transfer and expression of a gene in mouse is suggestive of applicability in humans, but does not provide evidence for the prediction of success of the procedure in humans.

Applicants argue that enough information was provided in the specification to demonstrate that cardiovascular conditions in humans could be cured by the same gene transfer methods used to express β-gal in mice. Applicants state they "...observed high levels of transduction... At 2,4, and 8 weeks , the levels of cardiomyocytes observed expressing β-gal was, <1% about 40% and >50%. Thus Applicants have clearly demonstrated stable and efficient transduction of transgenes..." Examiner submits that

Applicants have clearly demonstrated the transfer of a gene to mice, but have not convincingly shown that this method predicts successful gene therapy in humans. Furthermore, the ability to merely express a gene involved in a disease state does not a priori indicate the alleviation of that disease state can be achieved. Applicants have not even used a mouse model of a human disease state or a human gene to demonstrate there invention, yet claim that their methodology could routinely be practiced in humans.

Applicants hold that the delivery of any transgene to a cardiomyocyte is enabled by the observation that claimed rAAV vectors can mediate the transfer of the β-gal gene. This gene transfer event yields "...a sufficient biologic response therapeutically-effective to treat a cardiovascular condition targeted by the selected transgene." In support of this argument, Applicants interpret Crystal (Science (1995) 270:404-410) as providing evidence that gene therapy can be readily accomplished by one of skill in the art. They point to the examples in Crystal of experiments having to do with the treatment of several genetic disease states. It is important, however, to note that Crystal speaks of successful gene transfer, not gene therapy. The experiments cited therein are only suggestive of successful gene transfer and cannot be interpreted as examples of successful therapy. Indeed, Crystal states: "No human disease state has been cured by human gene transfer, and it is not clear when this will be accomplished." Clearly, Crystals position is that human gene therapy is not a routine (or even proven) methodology.

In support of there arguments, Applicants provide the disclosures of Kessler et al (Proc Natl Acad Sci (1996) 93:14082-87) and Pudakoff et al (Patent No. 5,858,351) as

examples of successful gene transfer to skeletal muscle of mice. The results and examples of these disclosures are not disputed by the Examiner. The results and examples provided by these disclosures are, however, irrelevant to providing evidence that the instant application anticipates human gene therapy. Again, in these disclosures the evidence points to successful gene transfer into rats or mice. Central to the Kessler paper is the demonstration that in a specific strain of mouse, the human erythropeitin gene can be transferred and expressed. The Applicants seem to interpret this as suggestive of the ability of gene transfer to treat Epo associated diseases in humans. It is not clear how one might be able to accurately calculate the level of recombinant gene expression in humans based on the expression of that gene in mice. Kessler et al does not suggest a means for determining this value. In addition, there is no way of knowing whether therapeutic amounts of Epo could be achieved in humans based on the data in mice. No basis for concluding that gene therapy in humans is predictable based on the state of the art is provided in these disclosures.

The disclosures of Hammond et al(Patent No's 6,100,242 and 5,792,453) and Leiden et al (Patent No 5,661,133) point to the further ability for genes to be transferred to rats and mice, however, there relevance is tangential to the instant application because the gene transfer methodologies outlined in these patents do not involve adeno-associated viruses. The characteristics of AAV mediated gene transfer are distinctly dissimilar from that of Adenoviruses and plasmid DNA, therefore, the information derived from the Patents of Leiden and Hammond cannot prove or disprove the effectiveness of AAV mediated gene transfer.

Applicants correctly point out that AAV is a suitable vector for gene transfer, that gene transfer to humans has been successful and that gene therapy is a productive area of research. These points, however, do not lead to the conclusion that gene therapy has been successful. Indeed, there is no scientific evidence extant definitely indicating that any form of gene therapy has had long term success in curing a human illness.

Applicants are also correct in noting that the safety of an invention does not fall within the purview of the Patent Office. Any arguments negating the Applicants invention based on safety issues are respectfully rescinded by the Examiner.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Christopher Drabik whose telephone number is 703-605-1156. The examiner can normally be reached on Monday-Friday from 9am to 5pm. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah Clark, can be reached on 703- 305-4051. The fax phone number for the organization where this application or proceeding is assigned is 703-308-4242.

Inquiries of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-1234. Questions regarding review of formality issues may be directed to Kim Davis, the patent analyst assisting in this application. She may be reached at 703-308-4242.

Deborah Clark

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